Supplementary Methods and Results

1. Literature search and data extraction
1.1 Methods
The following data points were collected for each patient from the primary publication:

- Sequencing method
- Pathogenic mutations in driver genes of pheochromocytoma and paraganglioma (defined by original publication) in SDHA SDHB, SDHC, SDHD, SDHAF2, FH, VHL, EPAS1, EGLN1, RET, NF1, TMEM127, MAX, HRAS, MET (germline excluded), FGFR1, CSDE1, MAML3). Clinical criteria of neurofibromatosis type 1 was considered as equal to NF1 germline mutation. Somatic mutations in TCGA were gathered from supplemental information in the primary publication, MET was not reported in the data supplement and was gathered from genomics data commons (https://portal.gdc.cancer.gov) release 9.0.
- Tissue status of pathogenic mutations (Germline/somatic). If both germline and somatic mutations in the same driver gene was available, the patient was categorized to have a germline mutation. If patient had a germline and somatic mutation in different driver genes the patient was categorized as having a germline mutation.
- Presence of pathogenic mutation in ATRX
- Location of primary tumor
  - Pheochromocytoma or paraganglioma
    - Head and neck or sympathetic paraganglioma
- Location of primary tumor
- Presence of metastatic disease with malignant disease considered equal to metastatic.
- Age (years)
- Gender (female/male)
- Tumor size, largest primary tumor diameter (mm)
- The hormone profile was classified as epinephrine, norepinephrine or dopamine:
  - Epinephrine if epinephrine/metanephrine above reference interval with norepinephrine/normetanephrine and dopamine/3-methoxytyramine within reference interval.
  - Norepinephrine if norepinephrine/normetanephrine above reference interval and dopamine/3-methoxytyramine within reference interval.
  - Dopamine if and dopamine/3-methoxytyramine above reference interval.
- Follow-up length (months)
- Survival status (dead/alive)
2. Bias assessment

2.1 Methods

(1) Patient selection;
   low bias, non selected group;
   high bias, selected group of patients not shown to be representative to the average in the community.

(2) Genetic assessment;
   low risk of bias, genetic variants obtained from original data and variant classification thoroughly described;
   high risk of bias, genetic information from secondary sources and/or interpretation of genetic variants not described.

(3) Genetic coverage;
   Low risk of bias, whole genome, exome or transcriptome sequencing. Algorithm based where those with negative results are subjected to above mentioned procedures.
   High risk of bias: targeted re-sequencing that do not cover all genes included in this study (fusion genes excluded)

(4) Definition of metastasis;
   Low risk: definition of metastasis accordingly to WHO 2004 or original information on disease extent provided.
   High risk: no definition provided.

(5) Hormone assessment;
   Low risk: laboratory values inclusive reference values are provided
   High risk: lack of laboratory values and/or reference values

(6) Follow up time, determined from median survival in the study cohort;
   Low-risk: >50% 120 months of follow up or death
   High risk: ≤50% 120 months of follow up and death did not occur
3. Genetic mutations
3.1 Results
SDHA, 8 patients (1.1%, 95% CI 0.6-2.2); SDHB, 58 patients (8.3%, 95% CI 6.4-10.5); SDHC, 3 patients (0.4%, 95% CI 0.1-1.2); SDHD, 9 patients (1.3%, 95% CI 0.6-2.4); SDHAF2, 1 patient (0.1%, 95% CI 0.0-0.8); FH, 1 patient (0.1%, 95% CI 0.0-0.8); VHL, 75 patients (10.7%, 95% CI 8.6-13.2); EPAS1, 24 patients (3.4%, 95% CI 2.2-5.0); EGLN1, 2 patients (0.3%, 95% CI 0.1-1.0); RET, 64 patients (9.1%, 95% CI 7.2-11.5); NF1, 103 patients (14.7%, 95% CI 12.3-17.5); TMEM127, 7 patients (1%, 95% CI 0.4-2.0); MAX, 9 patients (1.3%, 95% CI 0.7-2.4); HRAS, 57 patients (8.1%, 95% CI 6.3-10.4); FGFR1, 6 patients (0.9%, 95% CI 0.4-1.8); MET, 8 patients (1.1%, 95% CI 0.6-2.2); CSDE1, 5 patients (0.7%, 95% CI 0.2-1.7); and MAML3, 8 patients (1.1%, 95% CI 0.5-2.2). Twelve patients (1.7%, 95% CI 0.9-3.0%) had mutations in multiple different driver genes.
4. Genotype-phenotype correlations

4.1 Results

Pseudohypoxic PPGLs occurred more often in males, 100 patients (57.1%) versus females, 75 patients (42.9%). The observation was opposite in kinase signaling males, 90 patients (37%); versus females, 153 patients (63%); and wnt/unknown males, 117 patients (41.6%); and females, 164 patients (58.4%) [chi-square test p<0.001]. The catecholamine profile was also different in-between subtypes [chi-square test p<0.001]. Pseudohypoxic PPGLs were predominantly noradrenergic (52/71 patients; 73.2%) with a relatively large subset being only dopaminergic (10/71 patients; 14.1%). A majority of kinase signaling PPGLs had epinephrine secretion (88/109 patients; 80.7%). Wnt/unknown PPGLs showed a mixed catecholamine profile; epinephrine (64/144 patients; 44.4%), norepinephrine (69/144 patients; 47.9%) and dopamine (11/144 patients; 7.7%). PGLs occurred more frequently in the pseudohypoxic group (PGL, 101 patients; 57.7%; PPCs, 74 patients; 42.3%) compared to kinase signaling (PGLs, 6 patients; 2.5%; PCCs, 238 patients; 97.5%) and wnt/unknown (PGLs: 47 patients; 16.8%; PCCs: 233 patients; 83.2%; chi-square test p<0.001). Pseudohypoxic PPGLs were diagnosed at an earlier age (median 33 years) compared to kinase signaling (52 years) and wnt/unknown (50 years [Kruskal wallis test p<0.001]). Tumor size was also different; pseudohypoxia (median 40 mm), kinase signaling (46 mm), and wnt/unknown (51 mm [Kruskal wallis test p=0.0097]). The 4-molecular subgroups classification that split pseudohypoxia into TCA-cycle-related and VHL/EPAS1 related PPGLs showed a male overweight for both TCA and VHL/EPAS1 subgroups. Pseudohypoxic TCA-cycle related PPGL showed more frequent dopamine secretion and a higher frequency of PGLs than VHL/EPAS1 subgroup. VHL/EPAS1 were diagnosed at a younger age compared to TCA-cycle related PPGLs. Considering only patients with PPGLs that had somatic mutations in driver genes (VHL/EPAS1 vs kinase signaling), there was no gender difference. But, catecholamine production, localization (PPC/PGL), age and tumor size remained different. ATRX mutation status was different for; SDHB mutated, 19% (8/42) with ATRX mutation; versus SDHB wild type 2.1% (9/425, [P<0.001]). A difference was also noted in the 3-molecular subgroups classification; pseudohypoxia 8.7% (11/127) ATRX mutated, kinase signaling 1.2% (2/164) and wnt/unknown 2.3% (4/176 [P=0.002]). ATRX mutation status also distributed different in the 4-molecular subgroup classification; Pseudohypoxia TCA-cycle 16.4% (9/55) with ATRX mutation, pseudohypoxia VHL/EPAS1 2.8% (2/72), kinase signaling 1.2% (2/164) and wnt/unknown 2.3% (4/176 [P<0.001).
5. Clinical correlations with metastatic disease
There were 291 observations available to assess the impact of primary tumor size on the development of metastatic disease. The most informative cut-off for prediction of presence of metastatic disease was 50 mm: Receiver operating characteristic area under the curve 0.6 (95% confidence interval 0.5-0.7); sensitivity 56.8%, specificity 56.7%. Therefore, 50 mm was used as the cut-off for grouping patients based on tumor size for further analysis.